A319

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/70, 9/127, 31/19, 31/245

A1

(11) International Publication Number: **WO 96/01637**

(43) International Publication Date: 25 January 1996 (25.01.96)

(21) International Application Number: PCT/SE95/00760

(22) International Filing Date: 21 June 1995 (21.06.95)

(30) Priority Data:
9402453-6 12 July 1994 (12.07.94) SE

(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BRODIN, Arne [SE/SE]; Kämpevägen 24, S-151 54 Södertälje (SE). CARLSSON, Anders [SE/SE]; St. Göransgatan 80, S-112 38 Stockholm (SE). HERSLÖF, Bengt [SE/SE]; Brunbärsvägen 2, S-114 21 Stockholm (SE). NICKLASSON, Martin [SE/SE]; Bränningestrandsvägen 72, S-151 39 Södertälje (SE). RYDHAG, Lisbeth [SE/SE]; P1 1570 Hälleberga, S-150 23 Enhörna (SE).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: NEW PHARMACEUTICAL PREPARATION FOR PAIN MANAGEMENT

(57) Abstract

A new pharmaceutical preparation comprising one or more local anaesthetic agents, a polar lipid, a triacylglycerol and optionally water. The new pharmaceutical preparation is excellent for topical treatment of pain.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

NEW PHARMACEUTICAL PREPARATION FOR PAIN MANAGEMENT

Field of the invention

The present invention relates to a novel pharmaceutical preparation for use as a local anaesthetic for topical administration, to the use of said preparation and to a process for preparing said preparation.

Background of the invention

EMLA® cream is the only product on the market giving anaesthesia of intact skin. EMLA® cream is administered to the skin under occlusion for 60 minutes. In order to obtain faster onset of anaesthesia other local anaesthetic agents and vehicle systems have been tested (Refs. Freeman, et al., Pediatr. Anaesthesia 1993:3, 129). For tetracaine, an old well-known topical anaesthetic agent, there are several patent applications for different formulations, among them a cream and a patch (Refs. Woolfson and McCafferty, WO 88/09169 and Smith & Nephew, EP 0175609 respectively). WO88/09169 discloses an onset time of approximately 30 minutes for the tetracaine cream and EP 0175609 discloses an onset time of approximately 30-45 minutes for the tetracaine patch. None of these formulations are so far on the market.

Prior art

WO 93/19736 discloses a pharmaceutical composition containing a defined lipid system of at least two lipid components, at least one being amphiphatic and polar and one being non polar, and wherein the active agent is lidocaine. The problem that has been solved according to WO 93/19736 is the considerable difficulties in overcoming the poor bioabsorption of lidocaine.

WO 94/00127 discloses application of lipids and lipid formulations for the treatment of skin and mucous membrane diseases or disorders displaying epidermal hyperproliferation and disruptions of the barrier function.

EP 455528 discloses cosmetic and dermopharmaceutical compositions containing vesicles of a mixture of phospholipids and glycolipids.

FR 2692781 discloses a cosmetic composition containing sphingomyelin from milk or fish.

JP 05163153 discloses a sphingolipid composition, solving the problem with malodour and discoloration, giving a stable composition during storage. The sphingolipid composition can be used as a cosmetic base and in the field of medicines, e.g. as emulsion stabilisers, percutaneous promoting agents etc. The lipids are extracted from the brain.

Outline of the invention

Fig. 1 is a graph showing the solid fat content in the triacylglycerol used, as determined by solid-phase NMR.

We have now surprisingly found that the problem mentioned above, namely to obtain faster onset of anaesthesia, can be solved by the new pharmaceutical preparation according to the present invention. The object of the invention is thus to provide a novel, clinically and pharmaceutically acceptable preparation for dermal pain management.

By using the pharmaceutical preparation according to the invention it is possible to achieve pain relief with a faster onset of anaesthesia than what is possible to

achieve with classical topical anaesthetic agents. Another advantage with the pharmaceutical preparation according to the invention is that it is less skin irritating than topical local anaesthetic formulations according to the prior art. Still another advantage is that the hydrolysis of ester compounds such as tetracaine seem to be much slower in the lipid vehicle than in conventional formulations.

The pharmaceutical preparation according to the present invention comprises the following ingredients:

a) one or more local anaesthetic agents
b) one or more polar lipids
c) a triacylglycerol
d) optionally water

The amount of the local anaesthetic is in the range 1-40 %, preferably 5-10 %. The amount of the polar lipid is in the range 1-40 %, preferably 1-10 %. The amount of the triacylglycerol is in the range 60-95 %, preferably 50-85 %. The amount of water is 0-95 %, preferably 0-20%. All percentages are given as the percentage by weight of the total weight of the pharmaceutical preparation.

The local anaesthetic can be selected from tetracaine, lidocaine, prilocaine, mepivacaine, lidocaine/prilocaine, tetracaine/lidocaine, and other local anaesthetics and combinations thereof.

The polar lipid is preferably a sphingolipid. The sphingolipid can be ceramides, monohexosylceramides, dihexosylceramides, sphingomyelins, lysosphingomyelins, sphingosines or other suitable sphingolipids, or mixtures thereof. The polar lipid can also advantageously be a galactolipid. Preferable galactolipids are digalactosyldiacylglycerols and monogalactosylglycerols.

Preferably the sphingolipid is sphingomyelin or products derived from sphingomyelin. The sphingomyelin content is preferably established by chromatographic methods.

The sphingolipid can be extracted from mammals milk, preferably bovine milk, brain, egg yolk or erythrocytes from animal blood, preferably sheep. The sphingolipid may be synthetic or semisynthetic.

The sphingolipid being the polar lipid is related to the composition and structure of human skin lipids, specifically in the epidermis layer. Ceramides, a main lipid component of this layer, is believed to form an extracellular barrier between the cells of the epidermis. The ceramides are further believed to originate from biological processes inside the cells and may be a result of biochemical degradation of sphingomyelins or hexosylceramides. The use of a sphingolipid in the pharmaceutical preparation is therefore preferred from the point of view of biocompatibility of the preparation with the natural barrier of the epidermis.

The polar lipid can also be a galactolipid. The galactolipid can be extracted from almost any kind of glycolipid containing plant material. Preferred plant materials are seeds and kernels from grains and cereals, for instance wheat, rye, oats, corn, rice, millet and sesame. Oat groats as well as wheat gluten have a high lipid concentration and are therefore of advantage to use in the process of preparation.

The triacylglycerol used according to the present invention is preferably selected from palm oil or other natural oils with a similar solid fat content or melting range. When palm oil is selected, commercial palm oil is fractionated to specific mixtures of suitable triacylglycerols, based on the combination of mainly palmitic, oleic and stearic esters of glycerol respectively. It is important for the triacylglycerol mixture utilized in the pharmaceutical preparation to be very pure and free from other glycerides, such as mono- and diacylglycerols. Such purity is

preferably confirmed by established chromatographic methods, for example thin-layer chromatography or high-performance liquid chromatography. It is further important that the triacylglycerol mixture fulfils the bulk quality requirements for use in pharmaceutical preparations. Such requirements are for example oxidation status and content of free fatty acids. The triacylglycerol may also be synthetic or semisynthetic.

The triacylglycerol fractions are defined by the percentage solid fat content, determined by solid-phase NMR as described in IUPAC method no. 2150, 7th edition. Thus, in the temperature range 25-35 °C, the fractions should contain 0-50 % (w/w) solid fat, preferably 0-30 % (w/w). see figure 1.

The pharmaceutical preparation according to the invention is administered topically, and can be administered in form of an ointment, a cream or included in a patch.

Pharmaceutical preparations

The pharmaceutical preparations according to the present invention were prepared by melting the triacylglycerol in an open water bath at a temperature range of 40-70 °C. Thereafter the local anaesthetic and the polar lipid were weighed in a vial. The triacylglycerol was melted and transferred to the vial and the mixture was dispersed with an Ystral homogenizer at approximately 1000 rpm and at a temperature range of 40-70 °C for 2-4 minutes. The amount of water required to form a topically applicable formulation was added at room temperature and the formulation was mixed carefully.

The following examples describe in detail the pharmaceutical preparations according to the invention.

The sphingolipids used in examples 1-7 and 11 were sphingolipids purified from bovine milk containing 60 - 80 % sphingomyelins. The sphingolipids used in example 10 were sphingolipids purified from egg yolk, containing approximately 98 % sphingomyelin. The galactolipid used in example 9 was purified from oats.

Example 1	
Tetracaine	5%
Sphingolipids from milk	14.3 %
Palm oil fraction	80.7%
Example 2	
Tetracaine	25%
Sphingolipids from milk	4%
Palmolein	70%
Water	1%
Example 3	
Tetracaine	25%
Sphingolipids from milk	3%
Palmolein	52%
Water	20%

Example 4

Tetracaine	25%
Sphingolipids from milk	4%
Palmstearin	70%
Water	1%

Example 5

Tetracaine	25%
Sphingolipids from milk	3%
Palmstearin	52%
Water	20%

Example 6

Tetracaine	10%
Sphingolipids from milk	1%
Palmstearin	69%
Water	20%

Example 7

Tetracaine	10%
Sphingolipids from milk	10%
Palmolein	79%
Water	1%

Example 8

Tetracaine	5%
Palm oil fraction	95%

Example 9	
Tetracaine	25%
Galactolipids	22%
Palmstearin	33%
Water	20%

Example 10	
Tetracaine	5%
Sphingolipids from egg yolk	14.3%
Palm oil fraction	80.7%

Example 11	
Tetracaine	25%
Sphingolipids from milk	22%
Palmstearin	33 %
Water	20 %

Biological studies

Topical anaesthesia/analgesia during occlusion of intact skin in the guinea-pig was studied with lipid formulations of local anaesthetics, as a modification of the method originally described by Edith Bulbring and Isabella Wajda in J Pharmacol Exp Ther 1945: 85: 78-84.

Male guinea-pigs (Dunkin-Hartley strain), weight range of 300-400 g, were used. The hair was removed from the back of the animal with a depilatory (Opilca® Hans Schwarzkopf GmbH, Hamburg, Germany). The hairless and smooth skin

was washed with soap and water and the animal was kept in a cage under a desk lamp about two hours before experimentation. On pricking the back of the animal with a cannula (22G) (Kifa (with no point)) or a von Frey filament (4.74) (Semmes-Weinstein pressure aesthesiometer), a twitching of the skin was elicited. A circular piece of gauze (one up to eight layers) saturated with test formulation in a thin plastic cup (4.5 cm^2) was applied to the middle of the back. The cup was then covered with Self-adhesive (Fixomull® BDF Beiersdorf AG Hamburg, Germany) and the occlusion was finally protected with an elastic bandage. At the end of the application period the treated area was wiped with a tissue and then examined for signs of local irritation. The skin which had been in contact with the formulation was pricked with a cannula or a von Frey filament under constant pressure six times at different places and the presence or absence of the twitching response in the skin of treated area was noted. This procedure was repeated at regular intervals of five minutes.

The number of pricks not eliciting a response gave an indication of the degree of sensory anaesthesia or analgesia. Groups of two, three or six animals were used for each test formulation.

Results

For all formulations discussed below, the percentage of anaesthesia/analgesia was measured after 15 minutes of contact time under occlusion in the guinea-pig.

In spite of the short contact time, 15 minutes, a waterfree formulation of 5 % of the active drug, tetracaine in sphingolipids and palm oil gave approximately 80 % of anaesthesia/analgesia with a duration of more than 90 minutes (Example 1).

When compared to a similar formulation of 5 % of tetracaine in palm oil without sphingolipids, the percentage of anaesthesia/analgesia was approximately 40 % and the duration was less than 30 minutes (Example 8). From these examples it is obvious that the presence of sphingolipids reduce the onset time and extend the duration of anaesthesia/analgesia.

Further increasing the concentration of tetracaine to 10 % in the presence of sphingolipids, a more saturated triacylglycerol fraction, palmstearin and 20 % of water, resulted in 100 % of anaesthesia/analgesia with a long duration (Example 6).

Further increasing the content of tetracaine to 25 % and sphingolipids to 3 % in palmstearin, also resulted in a high percentage of anaesthesia/ analgesia (Example 4). Addition of 20 % of water to the pharmaceutical preparation according to Example 4, resulted in 100 % of anaesthesia/ analgesia with a long duration. To optimize the effect of the drug, the saturation of the triacylglycerol fraction and the water content of the formulation were important parameters.

Using a more well-defined sphingolipid from egg yolk containing approximately 98 % of sphingomyelins did not alter the effect of the active drug dramatically (Example 10). The sphingolipids used in the other examples were all extracted from bovine milk, containing approximately 60-80 % sphingomyelins. The difference between sphingolipids from bovine milk and egg yolk is obviously not a critical parameter for the effect of the active drug.

A comparison between formulations containing either sphingolipids or galactolipids gave approximately the same percentage of anaesthesia/analgesia at a constant amount of the active drug. The function of the polar lipids is dual, meaning that the polar lipids reduce the onset time and extend the duration of

anaesthesia/analgesia, and are also acting as dispersing agent or stabilizer of the formulation.

The best mode of performing the invention is at present considered to be the pharmaceutical preparation according to Example 6.

Conclusion

The polar lipids have at least two functions in formulations intended for dermal pain management. They reduce the onset time and extend the duration of anaesthesia, as well as being non-irritating. They are also efficient stabilizers or dispersing agents for pharmaceutical formulations intended for dermal anaesthesia.

CLAIMS

1. A pharmaceutical preparation comprising

a) 1-40 % of one or more local anaesthetic agents
b) 1-40 % of one or more polar lipids
c) 60-95 % of a triacylglycerol
d) 0-95 % water

and wherein the percentages are the percentages by weight of the total weight of the pharmaceutical preparation.

2. A pharmaceutical preparation according to claim 1, wherein the polar lipid is a sphingolipid.

3. A pharmaceutical preparation according to claim 1, wherein the polar lipid is a galactolipid.

4. A pharmaceutical preparation according to claim 1, wherein the polar lipids are a mixture of sphingolipids and galactolipids.

5. A pharmaceutical preparation according to claim 2, wherein the sphingolipid is a sphingolipid mixture with at least 1 % sphingomyelin.

6. A pharmaceutical preparation according to claim 3, wherein the galactolipid is a galactolipid mixture with at least 1 % digalactosyldiacylglycerol.

7. A pharmaceutical preparation according to claim 1, wherein the trigacylglycerol is defined by the percentage solid fat content, determined by solid-phase NMR in the temperature range 25-35 °C.

8. A pharmaceutical preparation according to claim 7, wherein the triacylglycerol is a palm oil fraction.

9. A pharmaceutical preparation according to claim 7, wherein the triacylglycerol is palmolein.

10. A pharmaceutical preparation according to claim 7, wherein the triacylglycerol is palmstearin.

11. A pharmaceutical preparation according to claim 1, wherein the amount of the local anaesthetic is 5-10 %, the amount of the polar lipid is 1-10 %, the amount of the triacylglycerol is 50-85 % and the amount of water is 0-20 %.

12. A pharmaceutical preparation according to claim 1, containing

Tetracaine	10%
Sphingolipids from bovine milk	1%
Palmstearin	69 %
Water	20%

13. A pharmaceutical preparation according to claim 1 for use in therapy.

14. A pharmaceutical preparation according to claim 1, for use as a local anaesthetic preparation.

15. A pharmaceutical preparation according to claim 1, for topical administration.

16. A pharmaceutical preparation according to claim 1, wherein said preparation is in form of an ointment or a cream.

17. A pharmaceutical preparation according to claim 1, wherein said preparation is incorporated in a patch.

18. Use of a pharmaceutical preparation according to claim 1, for the manufacture of a medicament with local anaesthetic effect.

19. A process for the preparation of a pharmaceutical preparation according to claim 1, wherein the triacylglycerol is melted at a temperature of 40-70°C, one or more local anaesthetic agents and one or more polar lipids are weighed in a vial, the melted triacylglycerol is added and transferred to the vial, the mixture is dispersed with a homogenizer at 40-70°C for 2-4 minutes and the amount of water required to form a topically applicable formulation is added and mixed.

20. A method for the relieving of pain, wherein a pharmaceutical preparation according to claim 1 is administered to a patient in need of pain relief.

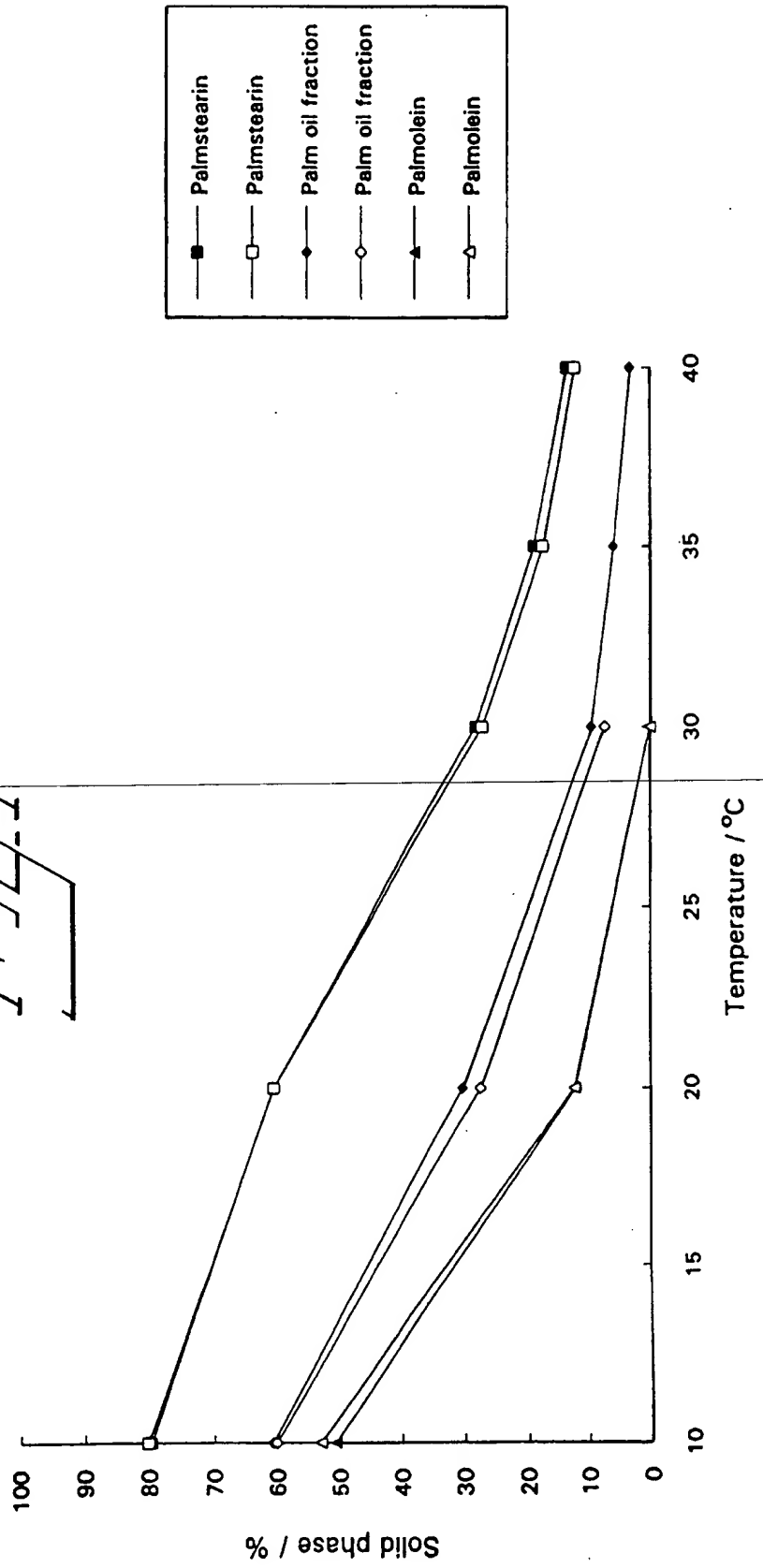
Palmstearin
Palmstearin
Palm oil fraction
Palm oil fraction
Palmolein
Palmolein
Solid phase / %
100
90
80
70
60
50
40
30
20
10
0
10
15
20
25
30
35
40
Temperature / °C

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00760

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/70, A61K 9/127, A61K 31/19, A61K 31/245
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI, IFIPAT, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STN International, File CA, Chemical Abstracts, volume 119, no. 7, 16 August 1993 (Columbus Ohio, US), Matsuzaki, Katsumi et al: "Development of a model membrane system using stratum corneum lipids for estimation of drug skin permeability", abstract no. 62449 & Chem. Pharm. Bull. (1993), 41(3), 575-9 --	1-19
A	STN International, File CA, Chemical Abstracts, volume 102, no. 4, 28 January 1985, (Columbus Ohio, US), Jackson, Patricia C. et al: "Anesthetics alter the lipid composition of barley-root membranes", abstract no. 3394, & Planta (1984), 162(5), 415-21 --	1-19

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 1995	23.10.1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00760

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9319736 A1 (KABI PHARMACIA AB), 14 October 1993 (14.10.93) --	1-19
A	WO 9400127 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA), 6 January 1994 (06.01.94) --	1-19
A	US 4610868 A (MICHAEL W. FOUNTAIN ET AL), 9 Sept 1986 (09.09.86) --	1-19
A	WO 9001323 A1 (BERNSTEIN, JOEL E. ET AL), 22 February 1990 (22.02.90) -- ---	1-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00760

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 20
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(IV): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 95/00760

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9319736	14/10/93	NONE	
WO-A1- 9400127	06/01/94	NONE	
US-A- 4610868	09/09/86	NONE	
WO-A1- 9001323	22/02/90	AU-A- 4216089	05/03/90